Published in final edited form as:

Am J Vet Res. 2013 January ; 74(1): 144–147. doi:10.2460/ajvr.74.1.144.

Effects of interstitial cystitis on the acoustic startle reflex in cats

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Abstract

Objective—To compare acoustic startle reflexes (ASRs) of healthy cats and cats with interstitial cystitis (IC).

Animals—28 healthy cats (11 males and 17 females) and 20 cats with IC (13 males and 7 females).

Procedures—To evaluate the effect of neutering on ASRs, ASRs in neutered and unneutered healthy cats were measured. To evaluate the effect of housing facility acclimation on ASRs in cats with IC, ASRs were measured in cats with IC within 1 month after arrival at the housing facility and again 2 to 3 months after arrival. To evaluate the effect of the environment on ASRs, ASRs were evaluated in all cats with and without IC after acclimation but before and then after environmental enrichment.

Results—Neutering led to a significant decrease in overall ASR in the healthy cats. Habituation to the housing facility resulted in a significant decrease in overall ASR of female but not male cats with IC. Environmental enrichment led to a significant decrease in ASR in cats with IC but not in healthy cats.

Conclusions and Clinical Relevance—The magnitude of the ASR appeared to be sensitive to environmental conditions and affected by sex, both in healthy cats and cats with IC. It was also higher in cats with IC versus healthy cats, except when cats were housed in a highly enriched environment.

Impact for Human Medicine—Treatment approaches that include reduction of a patient's perception of environmental unpredictability may benefit humans with IC.

Interstitial cystitis, also referred to as bladder pain syndrome in humans, is an idiopathic chronic visceral pain syndrome that affects humans and cats.^{1–3} In humans, the cause of IC remains speculative, and no generally accepted treatments are available.^{1,2} The cardinal urinary symptom of the disease in humans is pain, which is often associated with other symptoms perceived to originate from the bladder, including a sudden strong urge to void, increase in the frequency of urination, and nocturia.

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The characteristics of IC are remarkably similar between humans and cats. In addition to bladder-related symptoms or signs, affected individuals of both species have abnormalities of the urothelium, visceral afferent pathways, central and sympathetic nervous systems, and hypothalamic and gonadal hormone systems.⁴ The disease in humans can coexist with other chronic medical conditions, including panic disorder, post-traumatic stress disorder, fibromyalgia, and irritable bowel syndrome, which has led to the suggestion that these conditions may be manifestations of a so-called central sensitivity syndrome.^{5,6} Yunus⁵ proposed this term to describe patients with nonstructural disorders that have abnormally heightened responses to sensory stimuli. Evidence suggests that a comparable condition also may exist in cats.⁶

Altered sensitivity of CNS function may affect ASRs of affected individuals. The ASR is a brainstem reflex that responds to unexpected loud stimuli.⁷ It is a defensive response to sudden intense stimuli characterized in mammals by fast, involuntary eyelid closure and muscular contraction. The magnitude of the response can be altered by various experimental manipulations and is affected by many pathological conditions. Whether in humans or other animals, the ASR is similar to comparable stimuli, which may permit cross-species comparison of results. A heightened ASR has been reported for humans with other central sensitivity syndromes^{8–10} and in women with IC.¹¹

The purpose of the study reported here was to evaluate ASRs in cats with IC and compare the results with those of healthy cats. We hypothesized that because most cats with IC are neutered,^a the degree of ASR might be influenced by the lack of gonadal steroid hormones in neutered cats. Therefore, a second objective was to determine the effect of neutering on ASRs of healthy cats. Additionally, because environmental conditions can markedly influence the nature of clinical signs in cats with IC,¹² a third objective was to investigate the effect of acclimatization to a university animal housing facility on ASRs in cats with IC and the effect of environmental enrichment on ASRs in cats with and without IC.

Materials and Methods

Animals

Neutered adult cats with severe, recurrent IC were obtained as donations from US pet owners who had requested the cats be euthanized because of the intractability of the disease. Cats were transferred to The Ohio State University Teaching Hospital for confirmation of the diagnosis of IC and absence of other diseases. Healthy adult cats were obtained from a laboratory animal vendor. Interstitial cystitis was diagnosed on the basis of findings from current and past medical history and diagnostic evaluation (physical examination, CBC, serum biochemical analysis, urinalysis, urine bacteriologic culture, and cystoscopy).³ All urine samples were obtained by cystocentesis. Cystoscopy was performed on female cats with a 9F rigid pediatric cystoscope,^b and a 3F flexible cystoscope^c was used to examine

^aBuffington CAT. Effect of feline interstitial cystitis on acoustic startle response (abstr), in *Proceedings. 32nd Annu Meet Soc Neurosci* 2002;614.

^bKarl Storz Endoscopy America Inc, Culver City, Calif.

^cFive-Star Medical, San Jose, Calif.

male cats. The diagnosis of IC was made only when all published criteria for IC diagnosis were met.³

All cats were housed individually in stainless steel cages (70 × 78 × 75 cm) in rooms with 12 hours of light and 12 hours of dark in the animal-housing facility of The Ohio State University College of Veterinary Medicine and managed as previously described.¹² Cats were fed a commercial cat food^d in amounts sufficient to maintain a body condition score of 3/5, and free access to water was provided.

To evaluate the effect of neutering on ASRs in healthy cats, 28 healthy cats (11 males and 17 females) were used. To evaluate the effect of acclimation to the housing facility on ASRs in cats with IC, 20 cats (13 males and 7 females) with IC were used. To evaluate the effect of the environment on ASRs in cats with and without IC, 11 healthy neutered cats (5 males and 6 females) and 16 cats with IC (8 males and 8 females) were used. These cats were a subset of healthy cats and cats with IC from the previous evaluations. The study protocol was approved by the Animal Care and Use Committee of The Ohio State University.

Measurement of ASRs

A custom-built wooden chamber platform (35 × 70 × 2.5 cm) to which an open wire cage (20 × 29 × 26 cm) was securely attached¹³ was used during ASR assessments. The platform was attached with bolts to a plywood base at the corners with heavy compression springs in between. The bolts were tightened to apply pressure to the corners of the platform and base, yielding a highly damped connection.

A rod attached to the platform was lowered to just touch the center of the cone of a polypropylene speaker^e (diameter, 10.2 cm) secured to the bottom of the platform. Movement of the platform resulting from a startle response caused the rod to displace the speaker cone, which produced a voltage that was amplified through a preamplifier^f and amplifier,^g then digitized, recorded, and stored via data acquisition software.^h Startle amplitude was defined as the maximal peak-trough voltage generated within 200 milliseconds of the onset of the startle stimulus. Linearity of the platform response chamber was calibrated before each session through use of 4 to 7 small weights dropped onto the platform from a height of 20 cm.

Testing was performed in a room with a sound pressure level of 60 dB. Audio speakersⁱ (range, 70 to 20 kHz) were positioned approximately 12 cm from each end of the cage. The speakers were connected to an amplifier^j and delivered a computer-generated white noise acoustic pulse of varying intensity (80 to 120 dB), with a 2.5-millisecond rise and fall interval. The sound pressure level inside the chamber was calibrated before each session with a digital sound pressure level meter.^k

^dIams maintenance chicken-based dry formula, Dayton, Ohio.

^eRadioShack 4-inch midrange speaker, RadioShack Corp, Fort Worth, Tex.

^fGrass 7P1F preamplifier, Grass Instruments, Quincy, Mass.

^gGrass 7E Polygraph 5 X DC amplifier, Grass Instruments, Quincy, Mass.

^hWinDaq data acquisition software, Dataq, Akron, Ohio.

ⁱLabtec LCS-1070 stereo speakers, Labtec, Vancouver, Wash.

^jRadioShack 250-watt PA amplifier, Tandy Corp, Fort Worth, Tex.

For testing, each cat was moved to a small carrier ($53 \times 30 \times 36$ cm), carried to the testing room, and placed inside the box on the platform. This transfer was completed within 5 minutes after each cat leaving its home cage. Cats were given a 5-minute acclimation period once positioned in the startle cage, after which an orienting pulse of 118 dB was delivered, followed by a 118-dB acoustic pulse each minute for 15 minutes.

Experimental protocols

In the first study phase designed to evaluate the effect of neutering on ASRs, ASRs were measured in all healthy cats after at least 6 weeks of acclimation to the housing facility and again at least 3 weeks (range, 3 to 10 weeks) after neutering. In the second phase, because of the variable severity of lower urinary tract signs in cats with IC at the time of donation, ASRs were measured in 8 cats with IC within 1 week after arrival and in an additional 12 cats with IC within 1 month after arrival (range, 8 to 35 days; time 1) to minimize the risk of further exacerbating disease activity and compromising their welfare. The reflexes were measured again in all cats with IC 2 to 3 months after the initial startle session (time 2).

For the third phase, all participating cats had been acclimated to the housing facility and had their ASR measured at least once (range, 1 to 12 times) previously. The reflex was evaluated prior to and after a 14-day period in which environmental enrichment was provided. This enrichment consisted of care by the same investigator (JLS), daily provision of food treats, supervised time to explore outside the cage for 15 minutes, and extra time (15 minutes) for interaction between each cat and the investigator.

Statistical analysis

Mean startle amplitude for each cat was calculated by averaging the individual responses to the acoustic pulses. Response to the first (orienting) pulse and responses with values > 2 SDs from the mean response (which were never more frequent than 1/session) were excluded from the analysis. Because the data were not all normally distributed, logarithmic transformation was performed. Results were compared through 2-way ANOVA for treatment and sex. Significant interaction effects were investigated by performing a paired t test for simple main effects. All analyses were performed with commercial software.¹ Results are reported as mean $\pm$ SD; values of $P < 0.05$ were considered significant.

Results

Animals

All cats weighed between 2.5 and 7.0 kg. The mean $\pm$ SD age of the healthy cats was 1.8 ± 1.1 years for males and 2.1 ± 1.8 years for females; that of the cats with IC was 4.4 ± 2.8 years for males and 4.8 ± 3.0 years for females. Although the cats in the IC group were older than the healthy cats, no correlation between age and startle magnitude was identified in either group (data not shown). All healthy cats were domestic shorthair, whereas the donated

^kRadioShack digital sound level meter, RadioShack Corp, Fort Worth, Tex.

^lGraphPad Prism, version 5.0 for Windows, GraphPad Software, San Diego, Calif.

cats with IC consisted of domestic shorthair ($n = 14$), domestic longhair (3), Himalayan (1), Persian (1), and Snowshoe (1).

Effect of neutering on ASRs in healthy cats

Comparison of healthy cats before and after neutering revealed a significant effect of neutering on ASRs. Values were significantly ($P = 0.01$) lower after (2.55 ± 0.43 mV) versus before (2.77 ± 0.49 mV) neutering. No interaction effect or sex difference was evident.

Effect of acclimation on ASRs in cats with IC

No difference was detected between startle reflexes of cats with IC that were tested within 1 week versus 1 month after arrival to the housing facility, so these data were combined. Acute startle reflex values were significantly ($P = 0.007$) lower after acclimation to the facility (2.66 ± 0.51 mV) versus before acclimation (2.88 ± 0.46 mV). A significant ($P = 0.03$) interaction also was observed, related to a decrease in ASR for females (2.86 ± 0.49 mV vs 2.36 ± 0.34 mV) but not for males (2.89 ± 0.46 mV vs 2.83 ± 0.52 mV; $P = 0.50$).

Effect of environment on ASRs in cats with and without IC

A significant ($P = 0.01$) effect of health status (IC vs no IC) was identified with environmental enrichment, as well as a significant ($P = 0.02$) interaction. In this situation, the interaction resulted from a significant ($P = 0.02$) decrease in ASR in the cats with IC (2.73 ± 0.45 mV without enrichment vs 2.44 ± 0.36 mV with enrichment) but not in the healthy cats (2.32 ± 0.26 mV vs 2.22 ± 0.04 mV, respectively; $P = 0.24$). The ASR was significantly higher in cats with IC than in healthy cats before ($P = 0.02$) and after ($P = 0.03$) enrichment. No effect of sex was identified in either group (data not shown).

Discussion

The present study of ASRs in cats with and without IC yielded 3 main findings. First, neutering did not increase ASR values in healthy cats, making neutering an unlikely explanation for the greater ASR observed in cats with IC. Second, acclimation to the housing environment by cats with IC led to a decrease in ASR values in females but not males. Third, ASRs were responsive to environmental enrichment in cats with IC.

Because loss of reproductive hormones has been associated with alterations in autonomic nervous system function,¹⁴ some abnormalities found in cats with IC could be attributable to the loss of hormones associated with neutering, which has been suggested to be a risk factor for IC in cats.¹⁵ Gonadectomy generally leads to an increase in the ASR of male but not female rodents.¹⁶ In the healthy cats in our study, however, neutering led to a decrease in the ASR, such that responses were lowered by as much as 41%, which strongly weakens the supposition that neutering per se contributes to the risk of IC development. Although ASRs were measured after at least 6 weeks of acclimatization to the colony in the sexually intact cats, it is possible that further acclimatization may have occurred during the period between the first and second startle-testing sessions.

A sex effect on ASR also was found in cats with IC during acclimation to the colony environment. Whereas a significant overall decrease in ASRs was observed during acclimation, this was due solely to the decrease in ASR observed in the female cats. In contrast, male cats with IC had no similar effect. These results may suggest that although the prevalence of IC does not appear to be different in male versus female cats, male cats might respond differently to environmental enrichment or their ASR may be generally less responsive to external conditions. Although these possibilities were not explicitly tested in our study, comparable responses of animals of both sexes to environmental enrichment in laboratory¹² and clinical¹⁷ studies suggest that males may indeed be less responsive.

We also found that ASRs were further decreased in cats with IC but not in healthy cats when environmental enrichment was provided, although ASRs in the IC group were greater than those of the healthy cats whether before or after environmental enrichment. The lack of effect in the healthy cats may have resulted from a so-called floor effect, in that further reductions were not possible in the context of the study.

The increase in ASRs of cats with IC may have represented a heightened sensitivity to unpredictable events in their environment, as has been reported for humans with panic disorder and IC.^{8,11,18} We previously reported an increase in sympathetic nervous system activity in cats with IC consistent with noradrenergic dysregulation,⁴ as has been found in rodents subjected to unpredictable shocks and humans with panic disorder.⁸ An increase in unconscious activation of a defensive emotional circuit in the context of the threat of abdominal pain reportedly occurs in women with IC,¹⁸ and the pattern is similar to that previously reported for humans with anxiety, post-traumatic stress disorder, and irritable bowel syndrome.¹¹ These findings further support the face and predictive validity of IC in cats as a naturally occurring disease model of IC in humans and suggest the presence of central hyperexcitability in individuals of both species with the syndrome, at least in unenriched circumstances.

The finding of an abnormality in a patient population naturally raises the question of the relationship of the finding to the disease. The observation that the ASR was lower in female cats with IC after acclimation to the colony environment and in both male and female cats after versus before environmental enrichment suggests that an increase in ASR may be a consequence of the syndrome. A heightened ASR also occurs in humans with panic disorder, post-traumatic stress disorder, and generalized anxiety disorder, all of which are characterized by enhanced sensitivity to unpredictability.⁸ In patients with post-traumatic stress disorder, the enhanced ASR is believed to be a consequence of the syndrome rather than a familial risk factor.¹⁹

Limitations of the present study included the use of cats with IC so severe that it resulted in surrender by their owners, so the results might not apply equally to cats with milder IC. Additionally, nonsignificant results could have resulted from lack of statistical power, given the small number of cats used. Despite these limitations, however, the identified differences were consistent with clinical observations of heightened sensitivity to unpredictable events in cats with IC.²⁰ Furthermore, the beneficial effects of environmental enrichment observed

in the IC group raise the possibility for exploring therapeutic approaches that include reduction of perception of environmental unpredictability in humans with IC.²

Acknowledgments

Supported by the National Institutes of Health.

Abbreviations

ASR	Acoustic startle reflex
IC	Interstitial cystitis

References

1. Hanno P, Nordling J, Fall M. Bladder pain syndrome. *Med Clin North Am.* 2011; 95:55–73. [PubMed: 21095411]
2. Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol.* 2011; 185:2162–2170. [PubMed: 21497847]
3. Buffington CA, Chew DJ, Woodworth BE. Feline interstitial cystitis. *J Am Vet Med Assoc.* 1999; 215:682–687. [PubMed: 10476717]
4. Buffington CAT. Comorbidity of interstitial cystitis with other unexplained clinical conditions. *J Urol.* 2004; 172:1242–1248. [PubMed: 15371816]
5. Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Semin Arthritis Rheum.* 2008; 37:339–352. [PubMed: 18191990]
6. Buffington CA. Idiopathic cystitis in domestic cats—beyond the lower urinary tract. *J Vet Intern Med.* 2011; 25:784–796. [PubMed: 21564297]
7. Davis M. Neural systems involved in fear and anxiety measured with fear-potentiated startle. *Am Psychol.* 2006; 61:741–756. [PubMed: 17115806]
8. Grillon C, Lissek S, Rabin S, et al. Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiological marker of panic disorder. *Am J Psychiatry.* 2008; 165:898–904. [PubMed: 18347001]
9. Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. *Psychol Bull.* 2007; 133:725–746. [PubMed: 17723027]
10. Naliboff BD, Waters AM, Labus JS, et al. Increased acoustic startle responses in IBS patients during abdominal and nonabdominal threat. *Psychosom Med.* 2008; 70:920–927. [PubMed: 18842745]
11. Twiss C, Kilpatrick L, Craske M, et al. Increased startle responses in interstitial cystitis: evidence for central hyperresponsiveness to visceral related threat. *J Urol.* 2009; 181:2127–2133. [PubMed: 19286199]
12. Stella JL, Lord LK, Buffington CAT. Sickness behaviors in response to unusual external events in healthy cats and cats with feline interstitial cystitis. *J Am Vet Med Assoc.* 2011; 238:67–73. [PubMed: 21194324]
13. Heninger, GR.; Davis, M. Delayed effects of lithium on the somatosensory evoked response and the acoustic startle reflex in cats and monkeys. In: Gershon, S.; Schou, M.; Kline, NS., editors. *Lithium controversies and unresolved issues.* Amsterdam: Excerpta Medica; 1979. p. 841-853.
14. Stoney CM, Owens JF, Guzick DS, et al. A natural experiment on the effects of ovarian hormones on cardiovascular risk factors and stress reactivity: bilateral salpingo oophorectomy versus hysterectomy only. *Health Psychol.* 1997; 16:349–358. [PubMed: 9237087]
15. Willeberg P. Epidemiology of naturally-occurring feline urologic syndrome. *Vet Clin North Am Small Anim Pract.* 1984; 14:455–469. [PubMed: 6377663]

16. Toufexis D. Region- and sex-specific modulation of anxiety behaviours in the rat. *J Neuroendocrinol.* 2007; 19:461–473. [PubMed: 17504440]
17. Buffington CAT, Westropp JL, Chew DJ, et al. Clinical evaluation of multimodal environmental modification (MEMO) in the management of cats with idiopathic cystitis. *J Feline Med Surg.* 2006; 8:261–268. [PubMed: 16616567]
18. Kilpatrick LA, Ornitz E, Ibrahimovic H, et al. Gating of sensory information differs in patients with interstitial cystitis/painful bladder syndrome. *J Urol.* 2010; 184:958–963. [PubMed: 20643444]
19. Orr SP, Metzger LJ, Lasko NB, et al. Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure: association with posttraumatic stress disorder. *Arch Gen Psychiatry.* 2003; 60:283–288. [PubMed: 12622661]
20. Westropp JL, Kass PH, Buffington CAT. Evaluation of the effects of stress in cats with idiopathic cystitis. *Am J Vet Res.* 2006; 67:731–736. [PubMed: 16579769]